Remarks

Claims 1, 4-11, and 13-30 were previously pending and under examination. By this response no claims are currently amended; no claims are canceled; and no new claims are added. Accordingly, claims 1, 4-11, and 13-30 are currently pending and under examination. No new subject matter is introduced.

Provisional Obviousness-Type Double Patenting Rejection

The Examiner maintained the previous provisional rejection of instant claims 1, 4-11, and 13-30 under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claim 19 of copending Application No. 10/817,165. As previously indicated, Applicant is willing to consider filing a terminal disclaimer, if necessary, at the time that claims in the instant application are deemed to be otherwise in condition for allowance.

Rejections Under 35 U.S.C. § 112, first paragraph

The Examiner maintained the previous rejection of claims 1, 4-11, and 13-30 under 35 U.S.C. § 112, first paragraph, for alleged lack of enablement. More specifically, the Examiner asserts on page 3 of the final office action that the enabled method for treating asthma (murine model) comprising administering to a subject in need of such treatment an immunostimulatory oligonucleotide (8-100 nucleotides long) comprising SEQ ID NO:10 does not reasonably provide enablement for the ability to treat [atopic dermatitis] comprising administering to a subject in need of such treatment any immunostimulatory oligonucleotide (8-100 nucleotides long) having the claimed formula as shown in claims 1 or 5, or the broad scope of the possible CpG-ODN that are envisioned in the formulas of claims 1 or 5. The Examiner goes on to assert on page 4 of the final office action that the results shown for asthma do not indicate that the CpG will function in the same manner to treat [atopic dermatitis]. On page 6 of the final office action the Examiner asserts that one skilled in the art would not accept on its face the examples given in the specification as being correlative or representative of the successful treatment of [atopic dermatitis] in any organism comprising the administration by any route of any immunostimulatory nucleic acid comprising the formulas in claims 1 and 5 in view of the lack of

guidance in the specification and known unpredictability associated with the ability to predict the biological effects exerted by CpG containing oligonucleotides in any and/or all organisms. On page 7 of the final office action the Examiner goes on to assert that no correlation is taught in the instant disclosure between the ability of these CpG containing oligonucleotides to induce a Th1 response *in vitro* (e.g., amount of IL-6 induction) and their ability to treat a representative number of atopic conditions (i.e., [atopic dermatitis]) *in vivo*. Finally, the Examiner asserts on page 8 of the final office action that an assumed common mechanism of action does not ensure enablement for treatment.

In addition to the foregoing, which represent essentially a restatement of the prior grounds for rejection, the examiner asserts on page 10 of the final office action that it is not clear that the experimental data shown in the declaration [of Dr. Joel Kline submitted September 10, 2003] was achieved using any of the protocols set forth in the pending specification. Further, the examiner asserts on page 11 of the final office action that the success of treating atopic dermatitis with SEQ ID NO:10 [as demonstrated in the declaration of Joel Kline submitted September 10, 2003] is not necessarily representative or correlative of the ability to successfully treat any atopic condition or atopic dermatitis with the generic sequences claimed.

For reasons set forth below, Applicant respectfully disagrees and requests the Examiner to reconsider and withdraw her rejection under 35 U.S.C. § 112, first paragraph.

In respect of certain narrower grounds for rejection, Applicant points out to the examiner that the route of administration of oligonucleotide used in the experiments described in the above-referenced declaration of Dr. Joel Kline was intraperitoneal. Declaration, page 3, line 7 of Methods paragraph. It is respectfully submitted that intraperitoneal administration, which is specifically disclosed as a route of administration at line 10 on page 42 in the specification, is an embodiment of administering as currently claimed.

Without meaning to limit the claims further, Applicant points out to the examiner that the protocol for administration of CpG oligonucleotide used in the experiments described in the above-referenced declaration of Dr. Joel Kline was similar in many respects to the protocol

described in Example 12 of the instant application. More specifically, in each instance the protocol involved the administration of CpG oligonucleotide at the time of sensitization to allergen, followed by antigen challenge at a later time without concurrent CpG oligonucleotide administration.

Turning now to the broader grounds for rejection, Applicant first reiterates its arguments already made of record. The following remarks are offered to supplement those previous arguments with the purpose of convincing the examiner that the claims currently under examination are indeed adequately enabled by the specification. More specifically, Applicant urges the examiner to appreciate how the *in vivo* results disclosed for asthma, as well as additional *in vivo* and *in vitro* results disclosed in the specification, support the claimed methods for treating atopic dermatitis.

Applicant has described a class of molecules (oligonucleotides) having a common structural motif (a CpG dinucleotide) that when administered to a subject results in an aspect of the immune response being altered, with a Th1 response being favored. This class of oligonucleotides is described throughout the specification. The specification not only describes the ability of these oligonucleotides to produce a Th1-favored immune response (e.g., see page 7, lines 13-17; page 8, lines 13-15; and page 41, line 15 to page 42, line 3) but also presents *in vitro* and *in vivo* data using an adequate number of different CpG-containing oligonucleotides to satisfy the enablement requirement for the claimed invention.

The data in the application, including that represented in Tables 1-3, establishes that the unmethylated CpG is responsible for the immune stimulation. More than 40 oligonucleotides were tested. The data represented in Table 5 demonstrates that the immune stimulation has the characteristic pattern of a Th1 response. Eleven different oligonucleotides induced a Th1 cytokine profile, demonstrating the consistent stimulatory effect of CpG-containing oligonucleotides.

It is believed that CpG-containing oligonucleotides mimic bacterial DNA in their ability to promote an immune response. The inventors believed they discovered one of nature's pathways fundamental to the immune system. This discovery is described on page 35 of the specification under the heading "Teleological Basis of Immunostimulatory Nucleic Acids." It is taught that the stimulatory CpG motif, identified according to the invention, is common in microbial genomic DNA but quite rare in vertebrate DNA. Experiments described in Example 3, in which methylation of bacterial DNA with CpG methylase was found to abolish mitogenicity, demonstrated that the difference in CpG status is the cause of immune stimulation by bacterial DNA. It is further taught that "Teleologically, it appears likely that lymphocyte activation by the CpG motif represents an immune defense mechanism that can thereby distinguish bacterial from host DNA." Specification, page 35, lines 27-29.

Respecting asthma, a leading theory of asthma in 1996 was entirely consistent with the teachings of the present specification. The incidence and severity of asthma was steadily increasing in developed countries but not in developing countries. This increase in the developed countries was believed to be due in part to the steady decline of infectious diseases. This "Hygiene Hypothesis" of asthma posits that exposure to infectious organisms or exposure to antigens derived from these pathogenic organisms induce a T-helper 1 (Th1) response early in life, shifting the immune response of individuals with an allergic predisposition away from a T-helper 2 (Th2) response and towards a Th1 response (IL-12, IFN-γ), thereby conferring protection from developing asthma. It would have been believed that the synthetic CpG-containing oligonucleotides described in the instant application can invoke Th1 responses mimicking what occurs in nature, via infectious agents, to confer protection against asthma.

The specification includes *in vitro* data on mouse and human cells, as well as *in vivo* data. Tables 1-3 demonstrate that many different CpG oligonucleotides are capable of activating murine B cells and inducing cytokine expression in murine cells *in vitro*. Table 5 depicts an experiment in which multiple CpG-containing oligonucleotides were tested for their ability to induce cytokine expression in human cells. The experiment of Table 5 demonstrates that

numerous CpG oligonucleotides are capable of inducing cytokine expression and notably an IL-12 response. Data obtained in the *in vivo* experiments such as those shown in Table 4 and Example 12 is consistent with the data obtained in the *in vitro* experiments, confirming that the pattern of cytokine release and Th1 effects could be exploited *in vivo*.

The immune system in an asthmatic person, and likewise in a person with any atopic condition including atopic dermatitis, has cytokine activity that is imbalanced toward a Th2 response. One of ordinary skill in the art, appreciating the data discussed above, would have expected that CpG oligonucleotides would help restore a proper balance. More particularly, CpG oligonucleotides would have been expected to act on the immune system to bias the cytokine profile away from a Th2 response, and thereby be useful for treating asthma as well as any atopic condition including atopic dermatitis.

Example 12 confirmed that a CpG-containing oligonucleotide would have the ability to initiate *in vivo,* even in the presence of an antigen, a pattern of cytokine release which would drive the immune system toward a Th1 response and would treat asthma. Example 12 also confirmed that CpG not only shifts the cytokine response but also is effective in influencing important therapeutic aspects of asthma, such as infiltration of cells and fluid into the lungs. Based upon that teaching, persons of ordinary skill in the art would have believed that CpG oligonucleotides would bias the immune system toward Th1, when given alone and even when given together with an antigen which otherwise would provoke Th2 response.

To summarize thusfar, the disclosed ability of CpG-containing oligonucleotides to effect a shift away from a Th2 immune response, by itself, would be expected to be useful for treating not only asthma but also any atopic condition including atopic dermatitis. Furthermore, the disclosed ability of CpG-containing oligonucleotides to effect a shift towards a Th1 immune response, by itself, would be expected to be useful for treating not only asthma but also any atopic condition including atopic dermatitis. Further still, the disclosed ability of CpG-containing oligonucleotides to effect both a shift away from a Th2 immune response and a shift

towards a Th1 immune response would be expected to be useful for treating not only asthma but also any atopic condition including atopic dermatitis.

The Examiner has cited several papers in support of the lack of enablement rejection and in particular in support of the argument that the state of the art at the time of the invention was unpredictable. In respect of such papers, the following remarks are in addition to those already made of record.

McCluskie et al. 1999 and Krieg et al. 2000 have been cited for the proposition that biological responses to the administration of CpG containing oligonucleotides vary depending on the mode of administration and the organism.

McCluskie et al. describes DNA vaccines against Hepatitis B virus. On page 296, the page identified by the examiner, the reference mentions that one of the factors involved in influencing the Th bias of the response to DNA vaccines is the presence of CpG motifs. The reference is not relevant to the enablement of the pending claims because the pending claims do not encompass plasmid vectors (or DNA vaccines). The pending independent claims include limitations that exclude plasmid vectors (e.g., upper size limit of 100 nucleotides). The issues of predictability and therapeutic efficacy are very different for CpG oligonucleotides and DNA vaccines.

Krieg et al. is a review article describing the uses of CpG oligonucleotides. The office action specifically points to page 524 of this reference in support of the examiner's argument that biological responses to the administration of CpG containing oligonucleotides vary depending on the mode of administration and the organism. Applicant does not see this teaching in the reference. In fact the reference teaches on page 524 that "Unlike many vaccine adjuvants that have been extremely effective in mice but disappointing in humans, CpG DNA is also highly effective in higher primates." This teaching does not support the examiner's assertion that the administration of CpG oligonucleotides varies depending on the organism. Furthermore, Krieg

et al. describe the usefulness of CpG oligonucleotides in producing a Th1 biased immune response. Page 524 of Krieg et al. includes the following teaching:

> These and subsequent studies have shown CpG DNA to be a more effective Th1-like adjuvant than complete Freund's, and to be effective with multiple types of antigens and routes of immunization including mucosal immunization (reviewed in Ref. 50). In fact, in a comparison of 19 different adjuvants, CpG DNA was found to be the strongest for inducing Th1-like immune response to tumor antigens[51]. ...
>
> The potent Th1 adjuvant effect of CpG can even override preexisting Th2 immune responses[5,47]; it has been used as an adjuvant for allergy vaccines, where it induces Th1 responses to antigens in the presence of a preexisting Th2 response, leading to decreased symptoms following subsequent allergen inhalation ...

Weiner is cited by the examiner for the proposition that the molecular mechanism of CpG is unknown. Knowledge of the mechanism of action is not necessary, particularly in view of the detailed knowledge at the time the patent application was filed of the cellular effects of CpG oligonucleotides. The patent application identifies consistent changes in the immune system at the cellular level that occur in response to CpG administration and which are therapeutically relevant. Additionally, Table 1 of Weiner lists examples of cellular effects arising from immunostimulatory CpG ODN. A lack of understanding of the molecular mechanism does not render the cellular results unpredictable. Other statements in Weiner are consistent with enablement of the claimed invention. For instance it is taught on page 456 1st column second full paragraph that "Studies to date suggest CpG DNA could have significant therapeutic promise in the treatment of a variety of disorders, including infectious disease, allergy, and cancer." Page 457 under "*In vivo* effects of CpG ODN" teaches that "extensive studies have been done in rodents, and some studies have been done in non-human primates. The observed *in vivo* data fits well with the *in vitro* data outlined above."

The examiner cited Agrawal et al. in support of the assertion that the incorporation and positioning of chemical modifications relative to the CpG dinucleotide are highly unpredictable.

In particular, the examiner has identified pages 78-80 of Agrawal et al. as being particularly relevant. Agrawal et al. is a review article describing antisense oligonucleotides. The authors suggest on page 78 that in order to *reduce* non-antisense related activity it is best to avoid CpG motifs. The authors also indicate that if it is not possible to avoid CpG motifs, then it is possible to make one of three modifications to reduce the CpG activity of the oligonucleotide. One of the suggested modifications is to replace the cytosine base of the CpG with a 5-methyl cytosine base. The instant specification teaches that a CpG-containing oligonucleotide has an unmethylated C in the CpG motif. Further, the cited section of Agrawal et al. teaches that the proposed three modifications "significantly reduced side effects". Agrawal et al. does not teach that immune stimulation was abolished with any of these proposed modifications, just reduced.

Satoh et al. was cited by the examiner for the proposition that CpG was associated with dangerous side effects. The Satoh et al. reference is an abstract describing a study on the effects of CpG oligonucleotides administered subcutaneously to mice that are treated with 2,4-dinitrofluorobenzene (DNFB). It was concluded that CpG oligonucleotides were responsible for worsening of the allergic contact dermatitis (ACD) induced by DNFB. The issue of whether a drug is safe and has no side effects is not an appropriate test for enablement. Additionally, the teachings of the Satoh et al. reference are not sufficient to establish a lack of enablement for the claimed invention. The ACD is caused by DNFB treatment. The fact that CpG oligonucleotides may contribute to type IV hypersensitivity responses initiated by DNFB does not establish that CpG oligonucleotides would cause ACD in the absence of DNFB.

The Examiner cited Dziadzio et al. to support the assertion that the state of the art is "unpredictable with regard to the use of ISS-ODN in treating [atopic dermatitis]." (Office Action at page 6). However, Dziadzio et al. actually teaches that ISS-ODN, i.e., CpG-containing oligonucleotides, are encouraging as potential therapies for allergic disease. After summarizing several sets of data on page 280, Dziadzio et al. teach:

> These data suggest that ISS-ODN can induce a Th1 phenotype prior to allergen exposure. It appears that even without the presence of allergen, CpG motifs can induce a Th1 phenotype in multiple cell types including B cells, antigen-presenting cells (macrophages, dendritic cells), T cells, and NK cells. The expression of Th1 cytokines along with an upregulation of costimulatory molecules on these cells underscores the importance of ISS-ODN in Th1 and innate immune responses. The persistence of a Th1 response after antigen challenge in sensitized mice is encouraging as potential therapy for allergic disease. (page 280, 2nd-3rd full paragraphs).

The teachings of Dziadzio et al. as a whole thus do not support an assertion that the claimed invention was unpredictable at the time of filing of the patent application.

As described above, numerous working examples were provided in the specification. These examples in combination with the description in the specification were sufficient to enable one of skill in the art to practice the invention over the full scope of the claims. Consistent with these descriptions, a number of studies published since the filing of the patent application have reiterated, as set forth in the specification, that CpG oligonucleotides having different structures but maintaining the critical CpG motif result in an altered immune response. For instance, US Patent Application Serial No. 10/644,052, corresponding to U.S. Published Application No. 2005/0059619-A1 (cited in a previously filed Supplemental Information Disclosure Statement), describes numerous examples of CpG oligonucleotides that stimulate an immune response.

Thus, one of ordinary skill in the art, based on the teachings in the patent application, would have reasonably expected the claimed invention to work over the full scope of the claims.

In view of the foregoing, Applicant respectfully requests reconsideration and withdrawal of the rejection of claims 1, 4-11, and 13-30 under 35 U.S.C. § 112, first paragraph.

Conclusion

If, after reviewing this response, the Examiner believes that the application is not in condition for allowance, the Examiner is requested to call the Applicant's attorney at the telephone number listed below. If this response is not considered timely filed and if a request for an extension of time is otherwise absent, Applicant hereby requests any necessary extension of time. If there is a fee occasioned by this response, including an extension fee, that is not covered by an enclosed check, please charge any deficiency to Deposit Account No. 23/2825. No new matter has been added.

Respectfully submitted,
Krieg et al., *Applicant*

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